CHAPTER 1
CONFORMATIONAL MOBILITY OF THE B-RING IN SOME STEROIDS.
Although a simple cyclohexane molecule is capable of existing in several conformations, the important ones, which are well defined are the chair, the boat and twist conformations, I, II and III. Since the simple cyclohexane is very flexible and the energy of transformation from one to the other by rotation around the carbon-carbon single bond is not too high, it can pass through these conformations at room temperature, in solutions or in liquid state. However when bulky substituents are introduced into the ring or the cyclohexane ring is trans-fused to another, it rigidly holds its conformation. Thus in the normal tetracyclic and pentacyclic triterpenoids and steroids all the rings exist in the chair conformation. However, an end ring like A ring has some flexibility and in a transition state the ring can adopt a boat conformation, for purpose of a reaction although, normally it may be existing in the chair conformation.

This however is not the case with the ring B. The 3-ring of a usual steroid like cholestanol IV being trans-fused to the C-ring at C6, C9 on one side and again trans-fused to the 4-ring at C5, C10 on the other side, is more rigidly held and exists in a rigid conformation V. Hence values for the coupling constants of axial-axial, axial-equatorial etc. protons are often taken from substituents in ring B.
A double bond can be introduced into ring B, at six different positions, viz. 5,6 as in cholesterol, at 6,7 at 7,8 as in ergosterol and related compounds, at 8,9 as in triterpenes of the type euphol, lanosterol etc.; and at 9,10 and 6,10 by the migration of C\textsubscript{10} angular methyl group to an adjacent position.

The stable conformations in which a cyclohexene normally exists are the two alternate half chairs VI and VII and two alternate half boats VIII and IX. This is due to flexibility at the two carbon atoms further away from double bond, since the two carbon atoms involved in double bond and the two allylic carbon atoms are always rigidly held in one plane, due to the double bond. Applying this to the ring B of the steroid molecule, with 5,6 double bond, the carbon atoms that could be flexible are the ones at 8 and 9. But these being the positions of trans-fusion, between the B and C rings, are quite rigid and hence the cyclohexene formed by ring B with a 5,6 double bond can exist in one half chair conformation only.

In complete agreement with this, X-ray crystallographic studies have shown that cholesteryl iodide has its ring B existing in a half chair conformation. Similarly with a 6,7 double bond, the positions capable of flexibility are 9 and 10 but these are the positions of trans-fusion with the C and the A-rings, and hence are inflexible. The same is also the case with a 7,8 double bond, the carbon atoms 10 and 6 being
positions of trans-fusion with the ring-\(A\), with an 8,9 double bond 5 and 6 are the possible flexible positions, but 5 being the position of trans-fusion with ring \(A\), both are inflexible. The same is the case with a 5,10 double bond, where 8 is a position of trans-fusion with ring \(C\). Only in one position of the double bond, out of six possibilities, i.e. the one at 9,10, the carbon atoms involved are 6 and 7, both of which being not attached to any ring, have flexibility. Hence the cyclohexene formed by the introduction of this double bond is the only one in the \(B\)-ring which is potentially capable of a conformational flip from one to other of any of the half chair or half boat conformations.

A suitable compound which has a double bond in the required 9,10 position is a rearranged compound which Westphalen\(^2\) first obtained by treatment of cholestane 3\(\beta\)-5\(\alpha\)-6\(\beta\)-triol,3,6 diacetate (X) with acetic anhydride and sulphuric acid. After several attempts to elucidate its structure, this compound was finally shown to have the structure (XI). The position of the double bond being fixed on the basis of its U.V. absorption\(^4\) which indicated that the double bond was tetra-substituted and doubly exocyclic.

Since then several investigations have been made regarding the environment required for Westphalen rearrangement. These requirements may be summarised as follows:
XI

XII

XIII

a) $R = H$

b) $R = CO \cdot CH_3$  

c) $R = CH_3$

III d) $R = SO_3H$

e) $R = SO_2 \cdot CO \cdot CH_3$
1. The presence of a 3β-acetate is not 
essential for the rearrangement.

2. The cholesterol side chain does not 
effect this reaction.

3. It is absolutely essential to have 6α-
substituents which through 1-3 diaxial interactions 
destabilise the C10-methyl. It is however clear that 
the rearrangement is not restricted to the 3β-acetate.

4. It has been established by several 
experiments that mere creation of a carbonium ion at 
C5 is not sufficient for producing the rearrangement. 
It is significant that no rearrangement has been observed 
in the absence of a 5α-hydroxyl group.

After detailed investigations it has been established that rearrangement occurs only 
under two sets of conditions, viz. treatment with 
sulphuric acid and acetic anhydride and treatment with 
acetic anhydride containing potassium bisulphate.

It has been unambiguously established that in the first step there is sulphonation of the 
5α-hydroxyl by either, SO3, HSO3, OH-SO2-OAc/ is the 
one undergoing rearrangement. The reactions for the 
formation of these sulphonating agents and their subsequent 
reactions are represented below.
\[
\begin{align*}
\text{H}_2\text{SO}_4 + \text{CH}_2\text{O} & \rightarrow \text{OH-SO}_2\text{-OAc} + \text{AcOH} \\
\text{OH-SO}_2\text{-OAc} & \rightarrow \text{Ac-O-SO}_2\text{-OAc} + \text{AcOH}
\end{align*}
\]

Followed by breakdown of the mixed anhydride species,

either \[
\text{HO-SO}_2\text{-OAc} \rightarrow \text{SO}_3 + \text{AcOH}
\]
or \[
\text{HO-SO}_2\text{-OAc} \rightarrow \text{HSO}_3 + \text{AcOH}
\]

XII + sulphonating species \rightarrow \text{XIIa or XIIe}

Then \text{XIIa} \rightarrow \text{XIIb + HSO}_4 \quad \text{or}

\text{XIIe} \rightarrow \text{XIII + AcO-SO}_2\text{-OAc}

**Conformation of Westphalen diol-diacetate**

In an elegant series of experiments Jones and Summers converted Westphalen's diacetate (XI) by the scheme outlined in Chart I to Westphalen 3β-6α-diol 3-methyl ether (XIV). Oxidation of this compound furnished a ketone (XV) which on reduction with sodium and alcohol gave an oily product (XVI) different from the starting material. These workers presumed this to be an equatorial alcohol on the grounds that sodium alcohol reduction yields the more stable alcohol. As the Westphalen product has a β-hydroxyl group, the reduced compound (XVI) must therefore have the α-geometry. As the reduced product is α and equatorial the starting compound (XIV) must be β- and axial.
REACTION SCHEME OF JONES AND SUMMERS
In a comprehensive investigation, Narayanan and Iyer\textsuperscript{16} established beyond doubt that the Westphalen diol diacetate has the $C_3$-equatorial geometry. Furthermore, they also established that the geometry at $C_6$ is $E$. The arguments put forth by this group is as follows.

By an ingeniously devised scheme (Chart 2), this group obtained Westphalen's diol as the methyl ether at $C_3$ and the acetate at $C_6$ (XVII). From a comparative study of the I.R. spectrum of this compound with several suitably devised model compounds, these workers concluded that the $C_3$-acetate is equatorial as it shows one I.R. band at 1239 cm$^{-1}$ characteristic of an equatorial acetate, in contrast to the three bands observed for the axial acetates in this region.

These I.R. findings could readily be confirmed from the P.M.R. spectrum which gives a quartet for the $C_6$-proton at 4.8 p.p.m. with $J = 10$ and 5 cps. These couplings are those normally observed for an axial proton when it is coupled when it is coupled to an axial and an equatorial proton.

The findings of Narayanan and Iyer were later confirmed by M.M. Cannet et al\textsuperscript{17} who also demonstrated by P.M.R. that the $C_6^3$-acetate is equatorial. An interesting point made by these workers was that hydrolysis of Westphalen diol-diacetate (XI) results in preferential hydrolysis of the $C_3$-axial acetate in
CHART-2

Reaction Scheme of Narayanan and Iyer.
contrast to the normal rule of conformational analysis which would postulate a more easy hydrolysis of an equatorial isomer as compared to axial one.

Nevertheless one point remained to be established is that concern with the geometry of the compound resulting from sodium alcohol reduction. With a view to establish this, the present investigation was undertaken. This investigation revealed a very novel conformational mobility of the ring-B.

**PRESENT WORK**

As the conformation of the C₆-proton can be readily determined by the P.M.R. spectrum, it is necessary to distinguish this proton from that at C₃. This can be achieved if the substituent at C₃ would lead to a different chemical shift for the C₃-proton as compared to C₆-proton. In order to achieve this goal, it is necessary to have a methoxy group at C₃. As mentioned earlier two procedures can be used, one that of Jones and 15 Summers or the other that of Narayanan and Iyer. We followed the latter procedure as the yields obtained are better due to the fact that no selective hydrolysis is necessary. Thus by Scheme outlined in Chart 2 the Westphalen diol 63-acetate 3-methyl ether (XVII) was obtained. The spectral properties of this compound clearly showed that the acetate is equatorial.
Also the nature (narrow signal) of the C₃-proton revealed that this proton is equatorial. As the starting material has the C₃-proton axial, this indicated that the geometry of C₆ substituent has changed during rearrangement.

Hydrolysis of the Westphalen compound furnished the alcohol (XIV) (Chart 3) M.P. 107°; (c) 124° in agreement with that reported by Jones and Summers. The I.R. of this compound established the absence of an acetate group and displayed the hydroxyl absorption at 3580 cm⁻¹.

The P.M.R. spectrum of the alcohol could not be used to come to any conclusion regarding the geometry of the C₆- or C₃-proton as these were hidden by the methoxy methyl signal at 3.26 p.p.m.

Oxidation of the alcohol (XIV) yielded the ketone (XV) whose properties were identical with those reported by Jones and Summers. The I.R. spectrum revealed ketone absorption at 1725 cm⁻¹ while the P.M.R. spectrum showed essentially the same pattern for the C₃-proton (narrow signal at 3.49 p.p.m.). Its U.V. absorption at λmax 298 mµ shows a normal E max 18 of 55, indicating thereby that there is no appreciable overlap between the C₆ double bond and the C₆-carbonyl.

When this ketone was reduced with sodium and alcohol, it furnished an oily product, the T.L.C. of which showed that it was homogenous. As the Rₚ value for this reduced product is identical with that of the Westphalen alcohol M.P. 107° (XIV), it was
CHART-3

XVII

XIV

XV

XVI

XVIII

COMPOUNDS PREPARED IN PRESENT INVESTIGATION
indeed doubted whether this compound was homogenous. The P.M.R. spectrum of this compound displayed its C6-proton as a broadened signal at 3.4 P.P.M., the location of some of the methyl signals differed from those of the Westphalen alcohol.

In view of this we attempted to purify this compound through an acetate. The acetate obtained was an oil, but its T.L.C. (benzene + 5% pet. ether solvent Rf = 0.56, 0.53) showed that it was a mixture of two compounds, none of which corresponds to the starting alcohol. The faster moving spot corresponding to that of Westphalen's acetate (XVII).

A separation of this mixture using T.L.C. afforded both components in pure form. The faster moving compound M.P. 117° was identical in every respect (T.L.C., I.R. (Fig. 1) and N.M.R. (Fig. 2) with the Westphalen acetate (XVII).

The slower moving compound (XVIII) could not be obtained in crystalline form though its homogeneity could be clearly shown not only by T.L.C. in several solvent systems but also by its P.M.R. spectrum.

In the first instance these experiments clearly establish that the reduced product of Jones and Summers in all probability is non-homogenous. The I.R. spectrum of this compound (XVIII, Fig. 3) showed the absence of a hydroxyl group and the presence of an acetate function (1730 cm⁻¹, 1239 cm⁻¹). It could normally be anticipated that this acetate would be the axial isomer,
FIG. 2.

PMR SPECTRUM OF 3β-METHOXY 5β-METHYL 19 NOR - 5β-CHOLEST 9(10) EN 6β-ACETATE
but two pieces of evidence immediately cast doubt on this expectation. The first of these is that sodium and alcohol reduction usually yields the equatorial compound and the secondly that in T.L.C. the axial enimer is usually faster moving than the equatorial one. Though neither of these is in itself a rigid proof that this compound is not equatorial, together they cast doubt on the nature of the oily product.

The large molecular rotation difference (267°) between the two acetates also raised the suspicion that these compounds are not enimers.

The I.R. (CS₂ solution) (Fig. 4) of this oily acetate exhibits only one absorption band at 1239 cm⁻¹ a fact which has been clearly shown by Narayanan and Iyer to indicate an equatorial acetate.

In agreement with this expectation the P.M.R. of this compound (Fig. 5) displays signals for the C₆-proton as a quartet at 4.6 p.p.m. J = 11 and 4 c.p.s. which is due to the coupling of the C₆-hydrogen with the C₇-axial and equatorial protons respectively. The C₇-proton in this spectrum can be recognised as a narrow signal at 3.45 p.p.m. indicating its equatorial nature and demonstrating that the AB rings are still cis fused.

Hydrolysis of this oily acetate gave the corresponding alcohol (XVI) (α)D +15° which shows IR absorption at 3440 cm⁻¹ (ν - COOH)
FIG. 4 a. IR SPECTRUM OF 3β-METHOXY 5β-METHYL 19 NOR 5β-CHOLESTA 9(10) EN 6α-ACETATE (CS₂)

b. IR SPECTRUM OF 3β-METHOXY 5β-METHYL 19 NOR 5β-CHOLESTA 9(10) EN 6β-ACETATE (CS₂)
FIG. 5

PMR SPECTRUM OF 3β-METHOXY 5β-METHYL 19 NOR 5β-CHOLESTeryl 9(10) EN 6α-ACETATE
FIG. 6. IR SPECTRUM OF 3β-METHOXY 5β-METHYL 19 NOR 5β-CHOLEST 9(10) EN 6α-01
If one compares the molecular rotation differences observed on passing from the alcohol to the acetate with the examples of 6α-compounds, known in the literature\(^\text{19}\) (Table I), it became clear that a positive rotation differences is characteristic of a 6α-substituent - while a 6β-substituent is associated with a negative rotation difference. This therefore establishes that the new alcohol (XVI) and the acetate (XVIII) are α-oriented.

The Westphalen diol-diacetate has been recently shown to exist in the conformation (XIX) and these findings have been confirmed in the present investigation. It seems that in oxidation or in subsequent reduction there is ring flip into an alternate half chair conformation (XX) and that the oily acetate must therefore be in this alternate conformation which would have its C₆-substituent in an α-equatorial position (XXI). This therefore can be regarded as a very novel example of ring mobility in a fairly rigid skeleton. The only question now remaining to be decided is the geometry of the ketone (XV). The ketone naturally can exist in either of the alternate half chair forms (XXII) or (XXIII). If it exists in conformation (XXII), it should show a positive cotton effect as revealed by an octant diagram (XXIV) of a model of this compound. On the other hand, the conformation (XXIII) would give a strongly negative cotton effect as
### Table I

**MP contributions of 6-substituted 6β-steroids**

<table>
<thead>
<tr>
<th>6α-alcohol</th>
<th>-100</th>
<th>6β-alcohol</th>
<th>+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>6α-acetate</td>
<td>-87</td>
<td>6β-acetate</td>
<td>-62</td>
</tr>
<tr>
<td>difference</td>
<td>-13</td>
<td>difference</td>
<td>+69</td>
</tr>
</tbody>
</table>

**Molecular rotations observed**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>XVI</td>
<td>+65.4</td>
<td>XI</td>
<td>+532.5</td>
</tr>
<tr>
<td>XVIII</td>
<td>+143.4</td>
<td>XVII</td>
<td>+401.5</td>
</tr>
<tr>
<td>difference</td>
<td>-78</td>
<td>difference</td>
<td>+131.0</td>
</tr>
</tbody>
</table>
CONFORMATIONS OF ACETATES
CONFORMATION OF KETONE

XXIII

XXII

XXVI  R = Ac
XXVII  R = H
FIG. XXV. OCTANT PROJECTION FOR KETONE XXIII

FIG. XXIV. OCTANT PROJECTION FOR KETONE XXII
represented in the octant diagram (XXV). The O.R.D. curve* of the ketone shown in methanol a strongly negative cotton effect at 310 μm (ΔE = -6β). As the C.D. curve of the analogous compounds<sup>20</sup> (XXVI) and (XXVII) have been reported to show strong minus cotton effects at 297 μm (ΔE = -2.98) and at 296 μm (ΔE = -2.8) respectively. They also support our findings and suggest that the ketone (XV) should be existing in the conformation (XXIII) or in both conformations (XXII) and (XXIII), but not in conformation (XXII) alone. Naturally reduction of the ketone could therefore give rise to either C<sub>6</sub>-γ-equatorial alcohol or a mixture of equatorial alcohols from both possible half chair conformations. As both alcohols were obtained it may appear that the ketone can exist in both possible forms which have only slight difference in their energy content.

It can readily be seen from models that in conformation (XX) where C<sub>6</sub>-β-substituent is axial, there is considerable crowding and consequent non-bonded interactions at the β-face of the molecule due to the adjacent -C<sub>5</sub>-methyl, C<sub>2</sub>-axial substituent, C<sub>6</sub>β-H and C<sub>13</sub>-methyl. This crowding is partly relieved in conformation (XIX) wherein the C<sub>6</sub>-β-substituent which was surrounded in the previous conformation (XX) is now equatorial and no longer subject to these interactions.

* We are indebted to Prof. W. Klyne for this measurement.
When the oxidation to ketone occurs strain is relieved and there is very little to choose between either of the two conformations (XXII and XVIII) for the ketone.

After* the communication of our results the 17 French workers who had initially supported the findings of Narayanan and Iyer put forward evidence 22 to show that ring B exists in a boat conformation, the arguments put forth by these workers are summarised below:

(1) The sum of the couplings of the C6-proton with the C7-protons is 14 c.p.s. This suggested that ring B is in a boat rather than a chair form as in the case of the latter the sum of the coupling constants should be around 19.5 c.p.s. based on calculations made using Karplus' equation.

* In fact though our communication appeared in November 1966 whereas that of the French workers appeared in December 1966 and January 1967. The date of receipt of this first French communication was earlier than ours by a month.
(2) The fluorine spectrum of the Westphalen compound having a 6R-fluoro substituent (XXVIII) displays a doublet at 128.3 and 129.1 p.p.m.‡‡ Each component of this doublet appears as a sufficiently well resolved triplet. The total width at half height being 88 c.p.s. This width is made up besides a large coupling (\( J_{\text{gem}} = 50 \text{ c.p.s.} \)) and a minor coupling* (2 c.p.s.) of coupling with the vicinal 7\( \alpha \)- and 7\( \beta \)-protons. The sum of these vicinal couplings being \([28\cdot(58+2)] \) 36 c.p.s. as maximum vicinal coupling in the case of several fluorinated cyclohexane derivatives in the chair conformation is 11.7 c.p.s. These authors believed that the maximum sum of the coupling constant with vicinal hydrogens can only be \( \sim 23.4 \text{ c.p.s.} \). The observed value of 36 c.p.s. according to these authors is due to the ring \( B \) being in the boat conformation. In support of this argument they suggested that the sum of the coupling constants in this case is the same as that of compounds containing a fluorine atom in the five membered ring, in which

‡‡ Signals are measured in p.p.m. values using trifluoromethyl toluene as the internal reference.

* The minor coupling is due to long range coupling of the \( C_6-\alpha \)-methyl with fluorine atom. This coupling can be seen by splitting of the methyl group in the proton spectrum.
\[ J_{\text{vic}} \delta_p \text{ values of the order of 20 and 15 c.p.s. are reported. These authors therefore concluded that as in the five-membered ring compounds here also the dihedral angles between fluorine and adjacent hydrogens must also be 0^\circ \text{ and } 120^\circ. \]

(3) These authors believe the boat conformation to be more stable than the half-chair conformation as there is a heavy interaction between the 1\(\alpha\) and 1\(\beta\) hydrogens which are separated by a distance of 1.4\(\text{Å}\) in the chair conformation. This distance increases to 2.0\(\text{Å}\) in the boat conformation.

(4) Conformation of ring B in 6 fluoro and 6-acetoxy derivatives is the same, as the shift of 18-methyl on preparation of Westphalen compound from the starting material is in all cases the same, that is 0.12 c.p.m. downfield as compared to the unrearranged starting material.

In our opinion none of these arguments may be regarded as convincing evidence to rule out the half-chair conformation. In the subsequent paragraphs flaws in the arguments of these workers are presented.

(1) In a very detailed\(^{23}\) analysis of several compounds whose conformations have been well established, it has been shown that the sum of the coupling constants of an axial hydrogen with its vicinal neighbours is around 12 c.p.s. in case of both chair and boat derivatives.
This makes it unreasonable to suppose that if the sum of the coupling constants is 14 c.p.s., it would indicate that the compound exists in boat conformation.

Also the same authors observed that the difference in the coupling constant is larger in compounds of chair conformation than those of boat conformation. These results are presented in Table 2. It can also be pointed out that though observed coupling constants for vicinal coupling may have larger differences than the actual couplings examples in which the reverse is true are very rare indeed. Based on these arguments the observed coupling of 6 and 10 c.p.s. for the C6 proton could necessarily imply that the actual couplings may be 5 and 11; 4 and 12 etc., but not 6 and 10; 7 and 9; etc. Our observed coupling constants therefore favours the half chair in preference to the boat conformation.

(2) As regards to the fluorine P.M.R. spectrum two important objections can be raised namely that in fluorine spectra 1 mm corresponds to 13 c.p.s. In view of this and the fact that no expansion techniques were used by the French workers, it seems doubtful whether the line widths actually observed are in fact those reported. Thus a width of 6.7 mm. corresponds to a boat conformation whereas that of 6 mm. would suggest a chair conformation. In a slightly twisted conformation the difference would be therefore still smaller. This argument cannot be considered significant.
### Table 2

**Chemical shifts and coupling constants of 2-bromo-3-ketones**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conformation</th>
<th>( \delta ) ( p.p.m. )</th>
<th>( J_{AX} )</th>
<th>( J_{BX} )</th>
<th>( J_{AB} )</th>
<th>( J_{aa} + J_{ea} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXIX</td>
<td>Chair</td>
<td>5.12 2.68(1( \beta ))</td>
<td>5.7</td>
<td>13.4</td>
<td>-13.1</td>
<td>19.1</td>
</tr>
<tr>
<td>XXX</td>
<td>Boat</td>
<td>5.08 2.74(1( \alpha ))</td>
<td>11.1</td>
<td>8.1</td>
<td>-13.4</td>
<td>19.2</td>
</tr>
<tr>
<td>XXXI</td>
<td>Boat</td>
<td>4.54 2.67(1( \beta ))</td>
<td>7.6</td>
<td>12.4</td>
<td>-13.6</td>
<td>20.0</td>
</tr>
<tr>
<td>XXXII</td>
<td>Boat</td>
<td>4.37 2.56(1( \beta ))</td>
<td>8.0</td>
<td>12.4</td>
<td>-13.6</td>
<td>20.4</td>
</tr>
<tr>
<td>XXXIII</td>
<td>Chair</td>
<td>4.70 2.69(1( \beta ))</td>
<td>-</td>
<td>6.0</td>
<td>13.2</td>
<td>-13.0</td>
</tr>
</tbody>
</table>
XXX \( R_1 = Br \), \( R_2 = H \)

XXX \( R_1 = H \), \( R_2 = Br \)

XXXII

XXXIII
Secondly the number of examples of vicinal coupling in rigid system of F-H couplings are comparatively few.

As regards to the energy difference between the boat and half chair conformations, it seems rather surprising that the French authors have not considered the very important eclipsed interactions which exist in the boat form. As such interactions occur between C₆ and C₇, it can readily be realized that these interactions would considerably destabilize the boat form, furthermore as C₆ also bears a substituent, like the acetox group, these interactions will be more significant.

The elegant proof given by the French authors that the fluoro and acetox compounds both exist in the same conformation, makes this argument equally tenable for the fluore derivatives. Finally it can be pointed out that slight deformation can increase the distance between C₁₁ and C₁ hydrogens in half chair conformation to a distance approaching 2°ₐ. Of course this twisting would require some energy.

In a subsequent paper the French workers have shown that epoxidation of the epimer of Westphalen's alcohol furnishes an α-epoxide which is hydrogen bonded. They argue that this is possible in the boat form of this compound, but not so in the case of the half chair form (XXI) in which this alcohol is equatorial. It can be very readily seen that if there is a gain in energy through hydrogen bonding this alcohol could easily pass over
into the alternate half chair form, when it would become axial and close enough to hydrogen bond.

In case of Westphalen's alcohol the French workers report that a mixture of $\alpha$- and $\omega$-oxides are formed. Though they did not separate the mixture, they put forward arguments to show that the $\omega$-epoxide is not hydrogen bonded whereas the $\alpha$-oxide is. In this case also, it can be seen that the half chair conformation in which this hydroxyl becomes axial (XX) would also be able to form a hydrogen bond with the $\alpha$-epoxide but not the $\omega$-one. It is also seen that for the Westphalen alcohol the $\omega$-epoxide cannot be hydrogen bond in either of the conformations (XIX) or (XX).

In our opinion therefore these arguments in fact favour the half chair form, as in the boat conformation the distance between oxygen of the epoxide and the hydroxyl hydrogen is larger than in the case of the half chair forms where the hydroxyl group is axial. A change from one form to another due to the gain in the energy through hydrogen bonding is well documented.

Another very important argument which has not been considered by the French workers is the fact that the I.R. spectrum indicated that the acetate group in the Westphalen compound and its epimer is equatorial a position only possible in the two alternate half chairs, but not in a boat, in which the epimer of Westphalen's compound would be
see almost axial, a finding in contrast to the observations. In summing up it can therefore be said that in all possibility, the Westphalen compound and its epimer exist in alternate half chair conformations rather than the boat conformation though further work would be necessary to completely rule out the latter.
EXPERIMENTAL

General remarks

Melting points are uncorrected and have been taken in a Gallenkamp melting point apparatus. Optical rotations were determined in 1% chloroform solution on a Perkin-Elmer spectropolarimeter or a Carl Zeiss polarimeter. Ultraviolet spectra (alcohol solvent) were taken on a Perkin-Elmer model 360 spectrophotometer. Infrared spectra were recorded as Nujol mull unless otherwise stated, on a Perkin-Elmer Infracord or Perkin Elmer Model 221 spectrophotometer, maxima are reported in cm^{-1}. Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride solution, using tetramethyl silane as the internal standard. The chemical shifts are reported in δ p.p.m. (unless otherwise stated). Alumina used in chromatography was neutral and grade III.

Thin layer chromatography was carried out using the apparatus described by Gupta and Sukh Dev, on silica gel (~200 mesh) mixed with plaster of paris 15% as binder. Spots were visualised by spraying with concentrated sulphuric acid.

Pet. ether refers to the fraction boiling between 60-80°C.
Cholesteryl methylether\textsuperscript{16}

To a solution of cholesterol (2 g) in dry benzene (96 ml), potassium metal (1.1 g) was added and the mixture was refluxed for one hour with vigorous shaking at intervals to disperse the molten potassium into small globules. Methyl iodide (36 ml) was added and refluxing continued for three hours, when potassium iodide generally separated out. The reaction mixture was then cooled, methanol was added and the solvents were removed in vacuo. The residue was extracted 4-5 times with boiling pet. ether. The pet. ether eluates were filtered through a column of alumina (60 g).

The pet. ether eluates on crystallisation from acetone-methanol gave colourless long needles of cholesteryl methylether.

\textbf{Yield} \hspace{1cm} 1.5 g.

\textbf{M.P.} \hspace{1cm} 84^\circ \hspace{1cm} \textit{Lit.}\textsuperscript{27} 85^\circ \\
\textbf{[a]_D} \hspace{1cm} -48^\circ \hspace{1cm} \textit{Lit.}\textsuperscript{27} -46.8^\circ \\
\textbf{I.R.} 1196 and 1108 cm\textsuperscript{-1} (aliphatic ether)

Elution of the column with ether gave cholesterol (0.4 g) which was crystallised and identified by m.p. and mixed m.p.

Cholestane-3β-4β-6α-triol-3-methylether\textsuperscript{16}

To a suspension of cholesteryl methylether (1 g) in formic acid 80% (10 ml), hydrogen peroxide 33% (1.6 ml) was added slowly and the reaction mixture was kept for fifteen hours at room temperature. Hot water was added to the reaction mixture to destroy the excess of hydrogen peroxide,
cooling at 0° for 1 to 2 hours yielded a white mass which
was filtered and refluxed with 2.5% methanolic potassium
hydroxide (60 ml) for 6 hours. The reaction mixture was
poured into water and extracted with ether. The ether layer
was washed with dil. HCl, NaHCO₃ and distilled water, dried
over sodium sulphate and evaporated. A white solid was
obtained which on crystallisation from ether-methanol gave a
crystalline compound.

Yield 0.6 g.

M.P. 153° Lit. 28 164°

[α]D -6° Lit. 28 -5.8°

I.R. 3500, 3300 cm⁻¹ (hydroxyl)

33-Methoxy-5β-methyl 12 nor-5β-cholesta 9(10)en 6α-acetate ²²
(XVII)

The triol methyl ether (250 mg) (XVIII) and acetic
anhydride (2.5 ml) were heated on water bath for one and
half hours. Then glacial acetic acid (10 ml) and acetic
acid containing sulphuric acid (1 cc of acetic acid containing
the mixture
12 mg of H₂SO₄, 0.5 ml) was added and kept at room
temperature for one and half hours. Afterwards it was poured
into crushed ice and left overnight. It was extracted with ether
and the organic layer was washed with sodium bicarbonate
and water, dried and evaporated to obtain an oily material
which was chromatographed on alumina (8 g.)

Pet. ether, benzene (1:1) elution gave a white solid
which was crystallised from methanol thrice to obtain the
expected Westphalen acetate.

M.P. 120-121° Lit. 28 122°

[α]D +84° Lit. 28 +84°

I.R. 1750 cm⁻¹ (acetate)
3α-Methoxy 5α-methyl 19 nor 5α-cholest 9(10) en-6-one (XIV)\(^{28}\)

The rearranged product was refluxed with 5% methanolic potassium hydroxide for six hours, when the corresponding 6α-hydroxyl compound was obtained.

Yield quantitative.

M.P. 107° Lit.\(^{28}\) 108°

\([\alpha]_D\) +120° Lit.\(^{28}\) +118°

I.R. 3600 cm\(^{-1}\) (hydroxyl)

3α-Methoxy 5α-methyl 19 nor 5α-cholest 9(10) en-6-one (XV)\(^{15}\)

The above compound (450 mgs) in pyridine (4 ml) was treated with chromium trioxide (460 mgs) in pyridine (4 ml). After twenty-four hours at room temperature the product was worked up as usual to obtain oily material which was chromatographed over alumina. Benzene elution gave a white solid which was crystallised from methanol.

Yield 250 mgs.

M.P. 64° Lit.\(^{15}\) 64°

\([\alpha]_D\) -4° Lit.\(^{15}\) -4°

I.R. 1725 cm\(^{-1}\) (ketone)

Sodium-alcohol reduction of 3α-methoxy 5α-methyl 19 nor 5α-cholest 9(10) en-6-one (XV)\(^{15}\)

The methoxy ketone (400 mgs) in ethanol (10 ml) was refluxed with sodium (2.5 g) for two hours. Isolation of the product in the usual way gave an oil which was chromatographed on alumina (16 g). Elution with ether gave the product as an oil.
Yield 200 mgs

$[\alpha]_D^0 +20^\circ$  
Lit. $+22^\circ$  
I.R. 3400 cm$^{-1}$ (hydroxyl)

3β-Methoxy 6β-methyl 19 nor 6β cholest 9(10) en 6β-acetate (XVIII)

The above material (300 mgs) was acetylated using pyridine (2 ml) and acetic anhydride (2 ml) in the usual way. Work up gave an oil which on T.L.C. (benzene + 5% pet. ether) showed two spots ($R_F$ 0.63, 0.56) none of them corresponds to the starting material. The faster moving spot corresponds to the westphalen acetate.

A separation of this mixture using preparative TLC layer chromatography afforded both components in pure form. The faster moving compound (120 mgs) was identified as westphalen acetate by its M.P., I.R. and N.M.R.

The slower moving compound (60 mgs) could not be obtained in crystalline form, though its homogenity could be clearly seen not only by T.L.C. in several solvent systems, but also by its P.M.R. spectrum.

Yield 60 mgs.

$[\alpha]_D^0 +30.4^\circ$

Analysis:

<table>
<thead>
<tr>
<th>Found</th>
<th>Requires</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, 78.64</td>
<td>C, 78.58</td>
</tr>
<tr>
<td>H, 10.87</td>
<td>H, 10.99</td>
</tr>
</tbody>
</table>

C$_{30}$H$_{60}$O$_3$  
I.R. 1730 cm$^{-1}$ (acetate)
3\(^{\beta}\)-Methoxy 5\(^{\beta}\)-methyl 19 nor 5\(^{\beta}\)-cholest 9(10) en 6\(^{-}\)-ol (XVI)

Hydrolysis of 6\(^{-}\)-acetate (50 mgs) with 5% methanolic potassium hydroxide gave the pure alcohol as an oil.

Yield 30 mgs.

\([\alpha]_D = +15.5^\circ\]

**Analysis**

Found: C, 80.51%; H, 11.4%

C\(_{28}\)H\(_{48}\)O\(_2\) requires C, 80.7%; H, 11.6%

I.R. 3400 cm\(^{-1}\) (hydroxyl)
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